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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	

ART UNIT	PAPER NUMBER
	14

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No	Applicant(s)
09/026,459	Xu et al
Examiner	**Group Art Unit**
Ram Shukla	1632

X Responsive to communication(s) filed on *Dec 16, 1999*

This action is **FINAL.**

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

X Claim(s) *1-43* is/are pending in the applicat

Of the above, claim(s) *35 and 38-43* is/are withdrawn from consideration

Claim(s) _____ is/are allowed.

X Claim(s) *1-34, 36, and 37* is/are rejected.

Claim(s) _____ is/are objected to.

Claims _____ are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

X Notice of References Cited, PTO-892

X Information Disclosure Statement(s), PTO-1449, Paper No(s). *4 and 9*

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. Amendment filed 12-16-99 is entered.

2. Applicant's election of invention of group I, claims 1-34 and 36-37 in Paper No. 11 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 35 and 38-43 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 27-32 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Instantly claimed invention reads on host cells that have DNA segment that may a naturally occurring mutant of RB which would be present in an animal or in a human cell or any eukaryotic cell that is part of an animal or human.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-19, 23-32, 34, 36-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DNA segments disclosed in Seq ID No 28, 30, 32, 34, 36, 38, 40, 42,44, 46, 48, and 50 that encode mutant RB proteins (other than pRB94) that have deletions of 2-34, 2-55, 2-78, 2-97, 31-107, 77-107, 111/112, 111-181, 111-241, 181-241, 242-300 (disclosed in Seq ID 29,31,33, 35, 37, 39,41, 43,45,47, 49, and 51), expression vectors

comprising said DNA, host cells comprising said DNA , does not reasonably provide enablement for any and all DNA segments that encode any and all mutants of RB wherein any 1, 2, 25,100, 150, 300 amino acids of the N-terminal 1-300 amino acids in one or two sequence regions of the N-terminus have been deleted, expression vectors comprising said mutant DNA segments and host cells comprising said DNA segments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 1 recites a DNA segment that encodes a RB protein (other than pRB94) wherein the N-terminus of the protein has been modified. Claim 2-7 limit the invention of claim 1 wherein at least one, two, at least about 25, 100, 150, and 300 amino acids from the N-terminus of RB protein has been deleted. Claims 8 and 9 limit the invention of claim 2 wherein a list of 32 sequence regions (that may be 30, 50, 100 etc. amino acids long), within N-terminal 1-300 amino acids, have been deleted. Claims 10-12 limit the invention of claim 2 wherein at least about 2-34 and 76-112 or about 2-55, and 76-112 amino acids have been deleted. Claim 13 recites that the proteins encoded by DNA segments of claim 1 have increased biological activity compared to the wild type RB. Claim 16 limits the invention of claim 13 to a DNA segment wherein in at least a second mutation is present. Claim 19 limits the invention of claim 1 wherein at least one amino acid has been deleted and at least one amino acid has been mutated from the N-terminal region of the RB protein. Claims 23-26 recite that the DNA segments of claim 1 are under control of a promoter in a recombinant vector and the vector is an adenoviral vector that is comprised in an recombinant adenovirus. Claims 27-32 recite that the DNA segment of claim 1 is comprised within a host cell and such a host cell is an eukaryotic cell, a human cell, a tumor cell and is present in an animal or human subject. Claim 34 recites that the protein encoded by the DNA segment of claim 1 has at least about equivalent or increased biological activity in comparison to the biological activity of the wild type RB protein. Claims 36-37 recite a recombinant host cell that can be a tumor cell, comprising an isolated gene encoding a modified RB protein (other than pRB94) that have N-terminal modification.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an

artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. In the instant application, the invention is directed to DNA segments that encode mutant RB proteins wherein N-terminal amino acids in chunks of different length in one region of sequence or in two regions of sequence have been deleted. In another scenario, parts of one sequence region have been deleted along with mutation or deletions of residues in other region. The invention also recites expression vectors and host cells comprising said DNA segments wherein host cell can be present in an animal or human. However, the specification is not enabling for the claimed invention because the specification does not provide sufficient guidance as to how an artisan would have made and practiced the claimed invention commensurate with scope of the claims, without undue experimentation.

The specification is not enabling because the invention does not provide sufficient guidance as to how an artisan would have generated the innumerable number of DNA segments, expression vectors, host cells that comprise the DNA or host cells comprising said DNA segments present in animals or humans. On page 7 of the specification lines 26-30, continued through page 13, there is disclosure of the deletion mutants that are encompassed by the claimed invention. While an artisan can theoretically produce all these and other possible DNA segments by PCR using multitude of primers that would produce deletion mutants or point mutations or combinations of the two, how would an artisan know which one, two, 25, 30-- or so amino acids to change out of 300 hundred amino acids in different combinations. Furthermore, what criteria an artisan would have used in deciding which first sequence region would have a deletion and which sequence region would have had point mutation? Furthermore, how would an artisan have known whether any of such proteins would have had any function? And if the proteins did not have any function what would have been the utility of such non-functional mutants of RB, expression vectors comprising such DNA segments or host cells comprising such vectors? Additionally why would any artisan look for a host cell which would have a non-functional mutation in a host cell that may be present in an animal or in a human.

Yet another issue is: what would be the biological activity of the protein that an artisan would look for, will it be binding to promoter element or will it be growth suppression activity? The specification does not provide any guidance whether a protein that may bind to a promoter may

but that may not produce growth suppression activity or vice versa, will be considered biologically active. Furthermore, Claim 34 recites that the modified RB proteins are characterized by "at least about equivalent biological activity", of the corresponding wild type protein. What is at least about equivalent biological activity because about equivalent is a relative term and can be interpreted differently. For example, if a mutant protein has 50% promoter binding activity but 10% growth suppression activity compared to wild type, will it be considered at least about equivalent and what would be the utility of such a mutant that have only 10% growth suppression activity. The specification does not provide any guidance as to how an artisan would have decided what would have been the biological activity of the proteins produced by the vast array of mutants generated and how would an artisan have decided which residues to delete or mutate.

Regarding claims 29-33 that recite host cells comprising claimed DNA segments and wherein the host cells are comprised in animal subjects or human subjects or are human cells, the specification does not provide sufficient guidance as to what would have been the use of human cells that would have a non-functional mutant of RB or how would any artisan have known to look for a non-functional RB mutant in a tumor sample or a human subject.

In conclusion, the specification as filed is not enabling for the claimed invention because the specification does not provide sufficient guidance as to how an artisan would have addressed issues raised above and would have been able to make and use the claimed invention commensurate with scope of claims, without undue experimentation. Therefore, limitation of the scope of the claimed invention to DNA segments disclosed in Seq ID No 28, 30, 32, 34, 36, 38, 40, 42,44, 46, 48, and 50 that encode mutant RB proteins (other than pRB94) that have deletions of 2-34, 2-55, 2-78, 2-97, 31-107, 77-107, 111/112, 111-181, 111-241, 181-241, 242-300 (disclosed in Seq ID 29,31,33, 35, 37, 39,41, 43,45,47, 49, and 51) expression vectors comprising said DNA and host cells comprising said DNA is proper.

8. Claims 31-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 31-32 recite that a host cell comprising the DNA segment of claim 1 is present within an animal and that the animal is a human. Claim 33 recites the DNA segment of claim 1 in a pharmaceutically acceptable excipient.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. In the instant case, when the invention of claim 33 is interpreted in the light of the specification, which discloses methods of inhibiting cellular proliferation in a tumor that may be present in a human subject using the claimed DNA segments (see pages 17 and 18), claimed invention would encompass a pharmaceutical composition and gene therapy. Furthermore, the instantly claimed invention of claims 31 and 32 recite an animal cell or a human cell comprising the claimed DNA is present inside an animal or a human respectively. Since the claimed DNA is an isolated DNA or recombinant DNA, it is interpreted that the cell comprising the claimed DNA is used for providing encoded protein to the animal or human or for ex-vivo gene therapy. However, the specification as filed is not enabling for gene therapy because the art of gene therapy is highly unpredictable as recognized in the prior art and as discussed in following para.

As noted in previous para (para 5), the invention encompasses any and all DNA segments that would have encoded mutant RB proteins that would have had modifications at their N-terminal end and such modifications included deletion of variable length of segments from one or two regions of the sequence or a combination of deletion and point mutations in different regions of the encoded protein. However, as noted above, the specification does not provide sufficient guidance as to how would an artisan have made and used all these DNA segments. If an artisan did not know which mutants to make or which deletion mutants to make, how would an artisan have known how to choose which mutants to use for therapeutics purpose or for inhibiting proliferation of tumor cells. Furthermore, even if one had to assume that a mutant inhibited the proliferation of a tumor cell line in vitro, would such a mutant have worked in vivo in an animal or in a human because the results of in vitro studies are not correlatable with in vivo systems since

the milieu of factors in vitro and in vivo are very different. Furthermore, as discussed below, an artisan would not have know what vectors to use for treatment because it is known in the prior art that different vectors produce different expression levels and may also pose other limitations. such as immuno-stimulation by adenoviral vectors. The specification on pages 30-36 describes different vectors that can be used for DNA delivery to cells, however the specification does not addresses limitations of different vectors used for DNA delivery as discussed below and how these limitations would have been addressed.

The specification is not enabling for gene therapy using claimed polynucleotides because the art of gene therapy is highly unpredictable and because the specification does not provide suitable guidance as to how an artisan would have dealt with uncertainties and problems recognized in the art regarding the unpredictability of gene therapy in humans subjects.

Crystal (Crystal RG. Science 270:404-410.1995) assessed the state of the art of the gene therapy at the time the claimed invention was made. In the abstract, Crystal states"human gene therapy still faces significant hurdles before it becomes an established therapeutic strategy." Later on page 409, he summarizes the problems faced in the art of gene therapy, such as inconsistent results, extrapolation of studies in mice to humans, production, and vector. He states " all of the human gene transfer studies have been plagues by inconsistent results, the bases of which are unclear" (see para 3 in col 1 on page 409). He also adds that there are several examples wherein prediction of gene transfer studies in experimental animals have not be borne out in human trials (see para 4 in col 1 on page 409). He also raises the issue of production of vectors, free of aggregation, contamination and variability from preparation to preparation, some of the problems that must be overcome before large clinical trials can be initiated. Additionally, there is the issue of an ideal vector? Crystal argues that an ideal vector for gene therapy is conceptually impractical because the human applications of gene transfer are broad and the ideal vector will likely be different for each application (see col 2 on page 409).

The report and recommendations of the panel to assess the NIH investment in research on gene therapy (Orkin SH and Motulsky AG. Report and Recommendations of the Panel to Assess the NIH investment in research on gene therapy, 1995) has also raised similar concerns.

For example, the report states "while the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 recombinant DNA advisory committee (RAC) approved protocols." The committee further noted "significant problems remain in all basic concepts of gene therapy. Major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host".

In a more recent assessment of the gene therapy art, Verma and Somia (Verma IM and Somia N. Nature 389: 239-242. 1997) summarize " In principle, gene therapy is simple: putting corrective genetic material into cells alleviates the symptoms of disease. In practice, considerable obstacles have emerged." They further add " But the problems- such as lack of efficient delivery systems, lack of sustained expression, and host immune response reactions- remain formidable challenges" (see the abstract). Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is no single outcome that we can point to as a success story" (see first and second paragraphs in col 1 on page 239).

Anderson (Anderson WF. Nature 392 (SUPP):25-30, 1998) notes that since the approval of first clinical trial of gene therapy protocol in 1990, more than 300 protocols have been approved worldwide. He further adds, "The conclusions from these trials are that gene therapy has the potential for treating a broad array of human diseases and that the procedure appears to carry a very low risk of adverse reactions; the efficiency of gene transfer and expression in human patients is, however, still disappointingly low. Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene therapy protocol has been successful in the treatment of a human disease."

Finally, Clay et al (Clark TM et al. Pathology Oncology Research 5:3-15, 1999) look at the some of the technical and biological hurdles that need to be addressed in gene therapy trials and conclude "Unfortunately, no gene therapy trial to date has been conclusively proven to be effective in treating the targeted disease.....It is clear that greater emphasis should be placed in vector development and understanding the biology of gene therapy targets if we expect gene

therapy to be a viable option in the future..... Further advances will also be required in vector development and in establishing the optimum transduction conditions for target cells to enhance the efficiency of gene transfer and to provide prolonged gene expression."

Regarding claims 31-32, it is further noted that the specification does not provide any guidance as to whether the host cells comprising the claimed DNA will be producing protein and if so at what level and what would have been the effect on the animal or human subject. Furthermore, is the protein being secreted by the protein and whether it is transported to other locations and whether there would have been any effect of the encoded protein on these sites.

In conclusion, the specification is not enabling for the claimed pharmaceutical composition because the art of gene therapy is highly unpredictable in general. The specification has not provided any guidance as to how an artisan would have dealt with the art recognized difficulties related to the unpredictability of gene therapy.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 2-12,20 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The invention of claims 2-12, 20, and 34 has been summarized in para 5 above.

Claims 2 and dependent claims are vague and indefinite because they use the term "about" . For example, It is unclear what number would be considered about 2 or what place position would be considered about 370.

Claim 34 is vague and indefinite because it is unclear as to what would be considered "at least about equivalent biological activity".

Claims 10 and dependent claims are vague and indefinite because it is unclear what would be considered a first sequence region and a second sequence region , for example what criteria is used to differentiate the two regions.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1-7, 13, 20, 23, 24, 27-30 are rejected under 35 U.S.C. 102(b) as being anticipated by Ewen et al (Ewen et al. Cell 73:487-497, 1993).

The invention of claims 1-7, 23, 24, and 27-30 has been summarized in para 5. Claim 13 recites that the DNA segment of claim 1 encodes a modified RB protein that comprises at least a first N-terminal mutation and also has increased biological activity compared to the activity of the wild type RB protein.

Ewen et al teach a RB mutant wherein the N-terminal amino acids 1-373 have been deleted (figure 1). This prior art also teaches that expression vector that were used for expression of the 1-373 deletion mutant (called Large Pocket) in host cells (see plasmids in methods section on page 494, 3rd para in 2nd col). Ewen et al further teach that the large pocket RB protein has higher biological activity compared to wild type because it suppresses the growth of a tumor cell line SAOS-2 (see table 1, rows 1 and 7).

Therefore, the invention of claims 1-7, 13, 20, 23, 24, 27-30 is anticipated by Ewen et al.

13. Claims 1-7, 13, 20, 23, 24, 27-30 are rejected under 35 U.S.C. 102(a) as being anticipated by Antelman et al (Antelman et al. Oncogene 15:2855-2866, 1997.

The invention of claims 1-7, 13, 20, 23, 24, 27-30 has been summarized in para 5 and 10.

Antelman et al also teach a RB mutant wherein the N-terminal amino acids have been deleted to produce a protein called RB56 (see figure 1). They also teach expression vectors and host cells that express the mutant protein (see methods section). RB56 also has a biological activity of wild type RB and its biological activity is higher than the wild type protein (see figure 6 and discussion -2nd para of col 2 on page 2862 and 2nd para in col 1 on page 2863).

Therefore, the invention of claims 1-7, 13, 20, 23, 24, 27-30 is anticipated by Antelman et al.

14. Claims 21 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Dryja et al (EP 0259031, March 9, 1988).

Claim 21 is drawn to DNA segments of claim 2 that encode a modified RB protein comprising contiguous amino acid sequence of Seq ID No 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, or 51, encoded by Seq ID No 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, or 50 respectively.

Dryja et al teach a human RB DNA that encodes a RB protein. NT Sequence 442-2784 of Dryja et al has 100 percent sequence identity and similarity with the sequence disclosed in Seq ID No 36 (see enclosed sequence comparison with Accession No I05311). This segment of Sequence when translated will encode a protein that has 100 percent sequence identity and similarity with the sequence disclosed in Seq ID No 37 (see enclosed sequence comparison with Accession No I05311).

Therefore, the invention of claims 21 and 22 (pertaining to the DNA segment disclosed in Seq ID No 36 and that encodes Seq ID No 37) is anticipated by Dryja et al.

15. Claims 21 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Hong-Ji et al (US 5,496,731, 3-5-1996).

The invention of claims 21 and 22 has been summarised in para 12.

Hong-Ji et al teach RB genes and gene products. Sequence 1 of Hong-Ji et al in the region 124-2466 has 100 percent query match as well as percent identity with the sequence disclosed in Seq ID No 36 (see sequence comparison with Accession No I18496 in the cited patent). This region of sequence taught in Hong-Ji also encodes a protein that has 100 percent sequence similarity and identity with the sequence disclosed in Seq ID No 37 (see sequence comparison with Accession No I18496 in the cited patent).

Therefore, the invention of claims 21 and 22 (pertaining to the DNA segment dislcosed in Seq ID No 36 and that encodes Seq ID No 37) is anticipated by Hong-Ji et al.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dryja et al (EP 259031, 09 March 1988).

The invention of claims 21 and 22 has been summarised in para 12.

Dryja et al teach a DNA that has 99.9% sequence similarity in the sequence regions 121-166-2784, 234-2784, and 292-2784 with the instantly claimed DNA segment whose nucleotide sequence is closed in Seq ID No 30, 32, and 34 respectively. When translated these regions (166-2784, 234-2784, and 292-2784) would encode amino acid sequences disclosed in Seq ID No 31, 33, and 35 respectively, except the first methionine (see comparisons with the accession no I05311 disclosed in cited patent).

It would have been obvious to one of ordinary skill in the art at the time of the claimed invention to modify the DNA sequence of Dryja et al by including a methionine codon at the beginning of NT 166-2784, 234-2784, and 292-2784 sequence regions of Dryja et al to make

the sequences disclosed in Seq ID No 30, 32, and 34 respectively with reasonable expectation of success because it is well recognized in the prior art that one requires ATG as the initiation codon that encodes for methionine for translating a DNA sequence into protein and without this codon translation will not be initiated.

18. Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friend et al (Friend et al Proc. Natl. Acad. Sci. 84:9059-9063, 1987).

The invention of claims 21 and 22 has been summarized above.

Friend et al teach a RB DNA that has 99.9% sequence similarity and identity with the sequence disclosed in Seq ID No 28. This DNA sequence also translated to an amino acid sequence that has 100% amino acid sequence similarity and identity disclosed in Seq ID No 29, except for the first amino acid (sequence comparisons of Seq ID No 28 and 29 with the accession no M33647 in Friend et al).

It would have been obvious to one of ordinary skill in the art at the time of the claimed invention to modify the DNA sequence of Friend et al by including a methionine codon at the beginning of nt 105-3057 sequence regions of Friend et al to make the sequences disclosed in Seq ID No 28 that would encode the protein disclosed in Seq ID No 29 with reasonable expectation of success because it is well recognized in the prior art that one requires ATG as the initiation codon that encodes for methionine for translating a DNA sequence into protein and without this codon translation will not be initiated.

19. DNA Sequences disclosed in Seq ID No 38, 40, 42, 44, 46, 48, and 50, that encode the amino acid sequences disclosed in Seq ID No 39, 41, 43, 45, 47, 49, and 51 respectively are free of prior art.

20. No claims are allowed.

21. The Applicant's World patent (WO9837091, Aug 27 1998) is made of record because this reference teaches the DNA molecules and host cells comprising said DNA molecules of the instantly claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Thursday and every other Friday from 8:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on (703) 308-2035. The fax phone number for this Group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 305-0196.

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